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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,135	12/26/2006	Bernard Weill	292043US0X PCT	4938

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EXAMINER
RAE, CHARLESWORTH E

ART UNIT	PAPER NUMBER
1611	

NOTIFICATION DATE	DELIVERY MODE
09/18/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/583,135	WEILL ET AL.	
	Examiner	Art Unit	
	CHARLESWORTH RAE	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments, filed 05/20/08, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Status of the Claims

Claims 7-11 are currently pending in this application and are the subject of the Office action.

Substitute Specification

Receipt of the substitute specification received 05/20/08 is acknowledged.

Declaration under 37 C.F.R. 1.132

Receipt of the declaration of Bernard Weill, executed 6 June 2008, wherein the results of experiments conducted to study in vivo the effects of mangafodipir and other oxidative stress modulators on hematologic toxicity of paclitaxel and susceptibility of mice to bacterial infection are disclose, is acknowledged and made of record. Based on the study results, Mr, Weill concluded that mangafodipir (Fig. 1, C; mangafodipir was given in a dose of 10 mg/kg i.p. three times a week for one month to mice infected with the bacteria *Staphylococcus aureus*) inhibited tumor growth when administered alone to a similar extent as paclitaxel, and also slightly amplified the antitumor effect of paclitaxel. In addition, administering mangafodipir or N-acetylcysteine in combination

with paclitaxel abrogated the hematologic toxicity of paclitaxel (see Declaration, page 2, last para.). By contrast, mice treated with N-acetylcysteine alone developed larger tumors than untreated mice, and adding N-acetcylcysteine to paclitaxel abrogated the antitumor effect of paclitaxel (Fig. 1, D; see Declaration, page 4, last para. to page 5).

It is the examiner's position that the study parameters are not commensurate with the instant claims. First, claim 7 recites "wherein said method consists of administering ... a cytostatic and cytotoxic amount of mangafodipir;" however, mangafodipir was administered at only one dose level of 10 mg/kg. It is further noted that mangafodipir as recited claim 7 is administered alone (as oppose to being administered in a combination). Based on the study data, it appears that the dose studied was cytotoxic and not cytostatic. Applicant is invited to clarify this issue. Second, claims 8, 10, and 11 encompass the combination of mangafodipir and 5-fluorouracil; however, the mangafodipir + 5-fluorouracil combination was studied. To the extent that 5-fluorouracil is not a taxane, and claim 7 only requires the mangafodipir be administered by itself, the scope of the study results are not commensurate with the scope of the instant claims and are limited only to mangafodipir + taxane combination.

REJECTIONS

Claim rejections – 35 USC 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 USC 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 7-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7 and 8 recite the term “cytostatic and cytotoxic,” which renders the claimed subject indefinite because "cytotoxic" implies killing of a cell, which precludes the occurrence of a subsequent cytostatic event/effect. Alternatively, a cytostatic effect/amount by definition is not capable of causing a cytotoxic effect. Thus, these terms are considered to have mutually exclusive meanings.

Dependent claims 9 and 10 are rejected for the same reason as these claims fail to correct the deficiency of the claims from which they depend.

Claim rejections – 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 7 and 9 are rejected under 35 USC 102(b) as being anticipated by Federle et al. (Federle et al. Efficacy and safety of mangafodipir trisodium (MnDPDP) injection for hepatic MRI in adults: Results of the U.S. Multicenter phase III clinical trials. Efficacy of early imaging. Journal of Magnetic Resonance Imaging. 2000; 12:689-701) as evidenced by Teslascan. www.epgonline.org/viewdrug.cfm/letter/T/ language/LG0001/drugId/DR004013/drugName/TESLASCAN.

The rejection under 112, 2nd para. is noted.

Claim 7 recites "[a] method for inhibiting the proliferation and viability of tumor cells in a patient in need thereof, wherein said method consists of administering to said patient a cytostatic and cytotoxic amount of mangafodipir." Claim 9 recites "wherein the amount of mangafodipir administered to said patient is from 1 to 100 mg/kg/day."

Federle et al. teach that focal liver disease comprises discrete, space-occupying lesions of the liver and includes abscesses, cysts, and neoplasms (= tumor cells; page 689, lines 1-3). Federle et al. teach that the therapeutic options available for managing focal liver disease includes surgery, cryotherapy, chemotherapy, or radiation). Federle et al. teach mangafodipir trisodium of 5 μmol/kg was shown to enhance liver in normal healthy volunteers, which is 20-fold less than the 0.1 mmol/kg doses generally employed for gadolinium-based contrast agents (page 690, third full para.). Federle disclose results showing enhancement of the liver following injection of mangafodipir in metastatic colon carcinomas (= tumor cells), which means that said patients had existing tumors cells present prior to the administration of mangafodipir (page 695, col. 1, second full para., lines 11-15). Federle et al. disclose that even though mangafodipir trisodium predominantly enhances normal liver tissue, it is distributed proportionally to vascular perfusion, and other tissues e.g. metastatic tumors (page 699, col. 1, last para.). To the extent that the only active method step is the step of administering mangafodipir to a patient in need thereof (e.g. patient with metastic colon carcinoma), an artisan skilled in the art would envisage that the dose of mangafodipir trisodium of 5

μmol/kg as taught by Federle is an amount capable of performing the intended function (i.e. cytostatic or cytotoxic effect on tumor cells).

Teslascan reference is an evidenciary reference only to show that 10 μmol of mangafodipir trisodium = 6.91 mg mangafodipir i.e. 10 μmol/kg = 6.91 mg/kg mangafodipir.

For the above reasons, claims 7 and 8 are anticipated by the cited art.

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8, 10, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Federle et al. (Federle et al. Efficacy and safety of mangafodipir trisodium

(MnDPDP) injection for hepatic MRI in adults: Results of the U.S. Multicenter phase III clinical trials. Efficacy of early imaging. Journal of Magnetic Resonance Imaging. 2000; 12:689-701), in view of Towart et al. (WO 97/49390) as evidenced by Teslascan. www.epgonline.org/viewdrug.cfm/letter/T/ language/LG0001/drugId/ DR004013/ drugName/TESLASCAN.

Federle et al. do not teach mangadofipir in combination with an anticancer medicinal product as claimed by applicant.

Claim 8 recites [a] method for increasing the cytostatic and cytotoxic effects on tumor cells, and decreasing the cytotoxic effect on normal leucocytes of an anticancer medicinal product selected from among platinum derivatives, 5-fluorouracil, and taxanes, wherein said method comprises administering to a patient treated with said anticancer medicinal product, an antitumoral and leukocyte-protecting amount of mangafodipir." Claim 10 recite "wherein the amount of mangafodipir administered to said patient is from 1 to 100 mg/kg/day." Claim 11 recites "[a] pharmaceutical composition comprising mangafodipir and an antitumor agent selected among platinum derivatives, 5-fluorouracil and taxanes."

Towart et al. (WO 97/49390) teach that certain chelating agents, such as Mn(DPDP) and their chelates, are particularly effective in reducing the toxicity of antitumor agent, in particular anthracyclines and paclitaxel (= taxane; page 2, last para. to page 3, first para). Towart et al. exemplify a method of treating male mice comprising intravenously injecting with saline or 10 µmol/kg of MnDPDP (page 19, Example 3).

It would have be obvious to a person of skill in the art at the time the invention was made to add paclitaxel as taught by Towart et al. to the mangafodipir as taught by Federle et al. for its anti-tumor effects. One would have been motivated to add paclitaxel to mangafodipir because Towart et al. teach that MnDPDP and its chelates are particularly effective in reducing the toxicity of paclitaxel and Federle et al. teach mangafodipir, which contain the MnDPDP moiety. One would have expected to successfully combine paclitaxel and mangafodipir for increasing the cytostatic or cytotoxic effects on tumor cells, and decreasing the cytotoxic effect on normal leukocytes medicinal product because Towart et al. teach that MnDPDP/chelates are particularly effective in reducing the toxicity of paclitaxel.

Thus, a person of skill in the art at the time the invention was made would have found it obvious to create the instant claimed invention with reasonable predictability

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau, can be reached at 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http:pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 800-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

6 September 2008
/C. R./
Examiner, Art Unit 1611

/Sharmila Gollamudi Landau/

Supervisory Patent Examiner, Art Unit 1611